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Microreactors

New Technology for Modern Chemistry

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1 State of the Art of Microreaction Technology

The aim of this chapter is to define the field referred to as microreaction technology, to analyze principal advantages, to comment on these benefits, reviewing current achievements, to document the state of the art of industrial implementation, and finally to outline future developments.

1.1 Definition

1.1.1 Microsystems Termed Microreactor

In accordance with the term "microsystem", which is widely accepted, microreactors usually are defined as miniaturized reaction systems fabricated by using, at least partially, methods of microtechnology and precision engineering. The characteristic dimensions of the internal structures of microreactors like fluid channels typically range from the submicrometer to the sub-millimeter range. Some people also prefer the terms nanoreactors or milli-/minireactors for devices with characteristic dimensions at the lower or the upper boundary of this dimensional range. In this book, however, only the term "microreactor" will be used.

1.1.2 Structural Hierarchy of Microreactors

The construction of microdevices generally is performed in a hierarchic manner, i.e. comprising an assembly of units composed of subunits and so forth. This holds particularly for microreactors which are based on an architecture characterized by multiplying unit cells, the so-called concept of numbering-up [1, 2]. In the following it is aimed to commonly define different units which most often are assembled in microreactors.

Definitions with Regard to Structural Hierarchy

The smallest units of a miniaturized continuous flow system are *microstructures*, in the vast majority of cases referring to *channel* structures (see Figure 1-1). Usually parallel channels are combined to an array surrounded by inlet and outlet flow regions, sometimes referred to as headers. A typical single or multiple flow channel configuration of distinct geometric nature is named *element*. A typical example for a mixing element is an interdigital channel configuration. In some cases, elements can consist of chambers too, e.g. carrying additional microstructures such as pores.

A combination of an element, connecting fluid lines and supporting base material, is named *unit*. For instance, a mixing platelet with an interdigital structure and feed lines is a micromixing unit. In order to increase throughput, units may form a *stack*, e.g. a stack of catalytic platelets in a chamber of a gas phase microreactor. Alternatively, identical devices

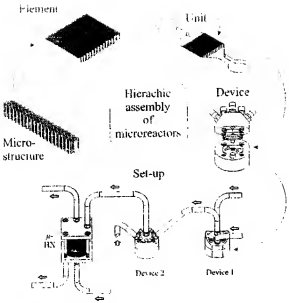

Fig. 1-1. Hierarchical assembly of microreactors, as evidenced for micromixer components.

can be arranged in parallel in a plane, e.g. a micromixer array consisting of thousands of unit cells.

Neither units nor stacks can be operated alone, hence, they are not real microreactors, since they need *housings* or, at least, *top and bottom plates* for fluid connection to external periphery. A *device* refers to a unit embedded either in a housing or between two end caps. The build-up of complex *systems* can be performed by integration of several units within one common housing. A system can also be based on a connection of devices, in this case referred to as *components*.

Any parallel or serial interconnection of components, systems or mixed combinations may be termed *set-up* or *plant*, dependent on the type of application, being lab- or industrial scale oriented, respectively. These set-ups or plants consist of either only microdevices or -systems, or, more likely, may contain microreactors next to conventional larger equipment.

Conceptual Division of Contents of This Book

The structural hierarchy – microstructure/channel, element, unit, device/component, system, set-up – is related to the conceptual division of the contents of this book. Chapters discuss components and systems with respect to different types of reactions and unit operations.

- Micromixers
- Micro heat exchangers
- Microseparators
- Gas phase reactors
- Liquid phase reactors
- Gas/liquid reactors

In the case of a combination of several operations, i.e. referring to a microsystem, the most characteristic function is chosen for classification. For instance, a system consisting of a mixer, heat exchanger and catalyst platelets, designated for carrying out gas phase reactions, will be discussed in the chapter "Gas Phase Reactors". The remaining components of this microsystem will not be described in separate chapters, e.g. in "Micromixers" or "Micro Heat Exchangers", except if they represent a unique flow configuration regarding their microelement. In this case, the presentation of the system is split into a chapter for the (unit) operation and a chapter for the system (reactor).

Very complex assembled microsystems including several types of reactors are discussed in separate chapters. These microreaction systems are referred to their respective type of application. Currently, two special fields of applications are of extremely high commercial interest, namely catalyst/material screening and energy generation. For these applications, two separate chapters were planned in this book. In addition, the assembly of several microsystems into a complete plant, e.g. for distributed production, is discussed in the Chapter 11 "The Miniplant Concept".

In the case of the description of components, sections refer to selected flow configurations, i.e. microelements, typical for a certain function. Since these elements are directly correlated to principles of function, e.g. a certain mixing concept, it was aimed to present a comprehensive overview of present approaches. Thereby, potential advantages of miniaturization are given practical application. Hence, a performance comparison of the various concepts, i.e. components or systems with specific elements, is crucial for a deep understanding of microreaction technology.

For instance, the chapter on micromixers is composed of sections, referring to the microelements termed with respect to the specific flow configuration. To illustrate this type of classification, the following examples of micromixing elements are given:

- Contacting of two substreams, e.g. in a mixing tee configuration
- Collision of two substreams of high energy and generation of a large contact surface due to spraying/atomizing
- Manifold splitting and recombination of a stream consisting of two fluid lamellae of two components

Subsections correspond to specific variants or adaptations of one concept, merely being examples which show the range of possibilities to realize a common idea. For instance, the section "Manifold Splitting and Recombination of a Stream Consisting of Two Fluid Lamellae of Both Components" is subdivided into the following subsections:

- Multiple Flow Splitting and Recombination Combined with Channel Reshaping
- Multiple Flow Splitting and Recombination Using Fork-like Elements
- Multiple Flow Splitting and Recombination Using a Separation Plate etc.

In the case of microreaction systems, this type of classification has not been followed, for reasons listed therein. For instance, in the chapter "Gas Phase Reactors" the microsystems were grouped according to the type of reactions carried out.

1.1.3 Functional Classification of Microreactors

Two classes of microreactors exist, referring to applications in analysis, especially in the field of biochemistry and biology, or chemical engineering and chemistry. Although these fields are distinctly different in most cases, as analytical and preparative equipment are, some microreactors cover both aspects. This holds particularly for combinatorial chemistry and screening microdevices which serve as analytical tools for information gathering as well as synthetic tools providing milligram quantities of products.

A further classification of microreactors is based on the operation mode, either being continuous flow or batch-type. The vast majority of microdevices presented in this book refer to continuous flow systems. Instead, batch systems such as micro and nano titer plates, e.g. for solid-supported chemical synthesis of drugs, will not be reported. In this field, the reader is referred to comprehensive overviews supplied by a number of excellent reviews and books [3–5].

The same holds for a large number of continuous flow microfluidic devices which were developed for analytical purposes starting in the late 1980s. If a series of processes such as filtration, mixing, separation and analysis is combined within one unit, the corresponding microsystems usually were termed micro total analysis systems (μTAS) [6–12]. Most often, these systems were applied for biochemical and chemical analysis. Modern developments consider e.g. polymerase chain reaction, electrophoretic separation, or proteome analysis, just to mention a few [13–15].

Concerning this field already comprehensively described [16], only component development will be presented in the framework of this book which turned out to be relevant for purposes of chemical microreactors. This is especially the case for analytical micromixers yielding a conceptual base for similar constructions for synthetic applications. Hence, in terms of consistency and novelty, the following chapters within this book will only refer to developments concerned with flow-through chemical microreactors, used for process development, production or screening.

1.1.4 Dividing Line Between Analysis and Reaction Systems

Reaction systems generally differ from analysis systems by producing or converting materials or substances. The latter devices are designed to gather information, e.g. to measure

the content of a certain analyte in a water sample taken from a lake. However, comparing extremely small individual systems, this difference apparently vanishes, because miniaturization of reaction devices ultimately will decrease the amount of converted materials to a level close to that of analytical devices. Therefore, the productivity of such small reaction devices, which is not sufficient anymore for synthesis purposes, can be used for process development or for screening only.

Both applications clearly refer to measuring tasks, the former regarding the finding of optimum process conditions, the latter of application-tailored materials. Actually, such measuring tools gather information similar to analytical devices. However, the purpose of using the information is distinctly different. In analytics, information gathering is an end in itself. For instance, the detection of ozone concentration in a certain layer of the atmosphere provides important information for ecological research. In contrast, information obtained in small reaction systems is used to optimize a lab synthesis or a large-scale process as well as to produce a new material with advanced properties, thus, finally is related to production issues. Hence, there is a clear dividing line between miniaturized analysis systems and microreactors for chemical applications.

1.2 Fundamental Advantages of Microreactors

Before analyzing the fundamental advantages of microreactors it is worthwhile to shortly review the benefits of miniaturized analysis systems, designed with similar characteristic dimensions as microreactors, and nano-scale reactors of much smaller size.

1.2.1 Fundamental Advantages of Miniaturized Analysis Systems

A large number of applications within the last decade clearly demonstrated fundamental advantages for miniaturized analysis systems compared to lab-scale equipment (see also Section 1.4.3). The smaller devices needed less space, materials, and energy and often had shorter response times [7]. In particular, more information per space and time is gained. By parallel microfabrication and automated assembly, the costs per device could be kept low. Decreasing the component size, in addition, allowed the integration of a multitude of small functional elements, thereby enhancing the system performance [7].

1.2.2 Fundamental Advantages of Nano-Scale Reactors

In the following, a nano scale reactor is defined as any supramolecular assembly which acts as a reaction unit, i.e. being a host providing a small reaction volume, sometimes accommodating only one molecule. To mention only a few, supramolecular assemblies such as molecular tweezers, zeolites, micelles, liposomes and Langmuir–Blodgett layers were, among other applications, utilized as small "reaction vessels". Most often, the molecular

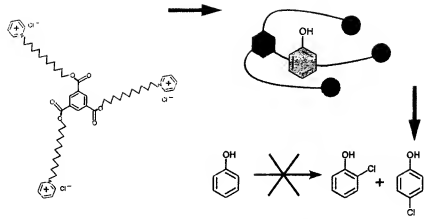

Fig. 1-2. Bola-type amphiphile forming a small nano-sized reaction vessel by means of self-organization. The chlorination of encapsulated phenol is thereby prohibited.

encapsulation strongly modified the reactivity of the reactants, e.g. by electronic interaction of π systems within a bola-type amphiphile [17], by adsorption and isolation in a zeolite cavity [18, 19], or by separation within micelles in order to prevent radical recombination [20].

Hence, small vessels, cavities and clefts provided in nanoreactors allow an interaction by means of molecular forces and modify the electronic structure of reactants. In addition, steric interactions are possible, e.g. influencing the conformation of a molecule or the free rotation of a group attached to a molecule. All these factors, known to modify the reactivity of "free" molecules as well, have a similar effect on "encapsulated" reactants. In this sense, nanoreactors behave like a solvent or a weak complexing agent.

To summarize, the most remarkable feature of nanoreactors is that they are actively changing chemistry, although the encasement certainly influences transport properties as well.

1.2.3 Advantages of Microreactors Due to Decrease of Physical Size

The volumes of microreactors are too large in order to interact with reactants significantly on a molecular level. Their main impact focuses on intensifying mass and heat transport as well as improving flow patterns. Therefore, benefits concerning chemical engineering is the main driver for microreactor investigations, while chemistry, in terms of reaction mechanism and kinetics, remains widely unchanged.

Decrease of Linear Dimensions

Decreasing the linear dimensions increases, for a given difference in a physical property, the respective gradient. This refers to properties particularly important for processing in chemical reactors, such as temperature, concentration, density, or pressure. Consequently, the driving forces for heat transfer, mass transport, or diffusional flux per unit volume or unit area increase when using microreactors.

These simple theoretical predictions were evidenced by a number of studies, e.g. concerning heat and mass transport. The majority of today's microreactor/heat exchanger devices contain microchannels with typical widths of 50 µm to 500 µm; the separating wall material between reaction and heat transfer channels can kept down to 20 to 50 µm, if necessary. As a result, heat transfer coefficients up to 25,000 W/m^2 K measured in microdevices exceed those of conventional heat exchangers by at least one order of magnitude [21]. Typical fluid layer thicknesses in micromixers can be set to a few tens of micrometers, in special configurations down to the nanometer range. Consequently, mixing times in micromixers amount to milliseconds, in some cases even to nanoseconds [22, 23], which is hardly achievable using stirring equipment or other conventional mixers.

Increase of Surface-to-Volume Ratio

As a consequence of the decrease in fluid layer thickness, the corresponding surface-to-volume ratio of the fluid entity is also notably increased. Specific surfaces of microchannels amount to 10,000 to 50,000 m^2/m^3, whereas typical laboratory and production vessels usually do not exceed 1000 m^2/m^3 and 100 m^2/m^3, respectively. Apart from benefits of heat transfer mentioned above, this increase in specific vessel surface can be utilized, e.g., in catalytic gas phase reactors coated with the active material on the inner walls.

Similar benefits have to be expected for multiphase processes, when at least one of the fluid phases has a layer thickness in the micrometer range. Both estimations by theory and experiments proved that the specific interfaces of such multiphases in microreactors can be set in the range of 5000 to 30,000 m^2/m^3. So far, the highest reported interface was measured using a falling film microreactor, amounting to 25,000 m^2/m^3 [24, 25]. Traditional bubble columns do not exceed a few 100 m^2/m^3; the best modern gas/liquid lab contactors such as impinging jets generate liquid surfaces of about 2000 m^2/m^3 [26]. In some favorable cases, e.g. regarding annular flow in micro bubble columns [25, 27], the corresponding specific interfaces can be set nearly as high as the specific surfaces of microchannels, thus potentially achieving 50,000 m^2/m^3 or even larger values. First measurements indeed showed large specific interfaces for this flow pattern, although not yet reaching the theoretically possible limit [25].

Decrease of Volume

Due to the reduction of the linear dimensions, the volume of microreactors is significantly decreased compared to large-scale reactors, typically amounting to a few µl. This difference becomes even larger when, in combination with reactor miniaturization, a large-scale batch process is replaced by continuous flow operation in microdevices. In case of a metallo-organic reaction, the material hold-up could be decreased from a tank of 6000 l size to a

volume of a few milliliters within five miniaturized mixers [28]. The smaller hold-up increases process safety and, due to shorter residence time, improves selectivity.

1.2.4 Advantages of Microreactors Due to Increase of Number of Units

A characteristic feature of microstructured fluidic devices is the multiple repetition of basic units, either fed separately in screening devices or operated in parallel, using a common feed line, for production purposes.

Fast and Cost-Saving Screening of Materials and Processes

Recently, the application of combinatorial strategies has been more and more extended from drug development in pharmacy [3, 4] to screening of inorganic materials, catalysts and polymers [29–32]. Whilst the former processing route was focused on the use of small batch reaction vessels, so called micro and nano titer plates, the latter approaches demand a diversification of reactor types. So far, inorganic materials, and in selected cases catalysts, were tested as arrays of spatially separated thin zones consisting of different materials [33, 34]. These zones usually were coated on wafers by means of thin film deposition techniques, in most cases using mask processes in order to locally change material properties, e.g. generating concentration profiles.

However, this straightforward approach is limited, especially regarding catalyst and polymer material research. The need for support porosity in the former case and long reaction times in the latter case are two among several arguments favoring the use of tube-like continuous flow reactors. A combined processing in many small tubes in parallel was already realized in flow-through tube reactors [35]. A further decrease in hydraulic diameter leads to more and more compact microreactor design.

First design concepts for such screening microreactors were a stack providing a frame for insertion of disposable catalyst carrier plates [31] and a sheet consisting of a number of reaction plates, structurally analogous to a titer plate [36]. Apart from increasing the number of samples to be investigated, further benefits in screening microreactors are the rapid and precise change of temperature, concentration and pressure. In particular, the possibility of isothermal operation and the high efficiency of mass transfer provide a sound information base, e.g. allowing to measure intrinsic kinetic properties.

Although currently screening in microreactors is most often performed by parallel processing, the continuous flow operation of microreactors enables rapid serial synthesis as well. One possible strategy can be based on the separation of liquid plugs containing the different samples separated by an immiscible liquid in a miniaturized channel [37, 38].

The generation of many samples, either by parallel or serial means, requires fast analysis. The integration of synthesis and analysis in one device has a number of advantages besides compactness. This serves to speed up analysis times, to save sample material and to eliminate additional sample transfer, either performed manually or by a robot.

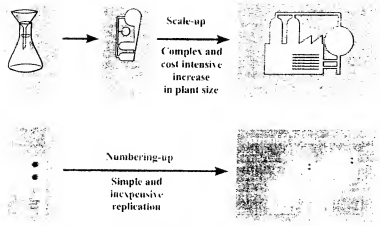

Fig. 1-3. Simplified scheme illustrating scale-up versus numbering-up strategies.

Due to this interdependence of sample generation and testing, screening is, among all application fields of microreactors, strongly dependent on the development of a practical total system approach, combining all relevant components in one device.

Production Flexibility

An increase in throughput in microreactors is achieved by a numbering-up approach, rather than by scaling-up [1, 2]. The functional unit of a microreactor, e.g. a mixing structure, is multiply repeated. Fluid connection between these units can be achieved by using distribution lines and flow equipartition zones, most likely hierarchically assembled (see also Section 1.1.2).

Numbering-up widely guarantees that desired features of a basic unit are kept when increasing the total system size [1, 2]. In an ideal case, measuring devices for process development and production reactor become similar, being composed of identical units. This ... demonstrated by comparison of mixing quality of an array of ten mixing units with the performance of a single unit [39]. However, these results also showed the crucial importance of flow distribution for the efficiency of the total reaction unit.

In addition, a larger number of units results in higher flexibility in adapting production rate to varying demand since, at least in principle, a certain number of systems can be switched off or further systems may be simply added to the production plant. A plant design based on a large number of small reaction systems can, again at least in principle, be modified to perform a variety of reactions by changing the piping network, i.e. the plant can be adapted to the synthesis of various substances using microreactor modules like a "LEGO" system. This flexibility may be supported by a considerably broader range of operating conditions of a microreactor compared with a macroscopic system.

1.3 Potential Benefits of Microreactors Regarding Applications

According to the discussion of the fundamental advantages, the following potential benefits regarding applications of microreactors obtain:

- Faster transfer of research results into production
- Earlier start of production at lower costs
- Easier scale-up of production capacity
- Smaller plant size for distributed production
- Lower costs for transportation, materials and energy
- More flexible response to market demands

Microreactors principally enable a faster transfer of research results into production due to their advantageous setting of operating conditions (see discussion above) yielding more precise data as well as information otherwise not accessible, e.g. regarding new process regimes. Meanwhile, this prediction has been confirmed by a number of examples of use [28, 40–42]. In addition, simple practical aspects make the use of microreactors as measuring tools attractive, e.g. ease and flexibility of construction and disassembly of experimental set-up, small material consumption, or faster approval due to enhanced safety.

Besides research transfer, the other potential applications presented above refer to production issues. So far, the corresponding technological development of respective microreactors could not reach a similar level as for measuring tasks. However, feasibility studies, mainly in the framework of bilateral industrial co-operations, are underway and soon will give a deeper insight [24, 43, 44]. The next steps in these developments will be the realization and testing of production microreactors. Currently, hydrogen production in miniaturized reformers, for subsequent use in fuel cells, seems to be one of the most promising fields that needs light-weight compact microreactors.

Facing production issues, throughput is directly correlated to reaction volume, whereas information gathering is independent of the size of the analysis system. Hence, it is usually assumed that specific production costs increase with decreasing reactor volume, referred to as economy of scale [45]. In addition, the ratio of construction material to reaction volume is inevitably high for microreactors, composed of a multitude of small channels separated by wall material. For similar performance of conventional and microreactors, this unfavorable ratio further seems to render production in microreactors unprofitable. However, specific fields have been identified where either the performance of microreactors is enhanced or the lower specific capacity is counterbalanced by cost saving due to other factors. Some of these fields refer to:

- Replacing a batch by a continuous process
- Intensification of processing
- Safety issues
- Change of product properties
- Distributed production

Replacing a Batch by a Continuous Process

At present, a number of processes are carried out batch-wise, e.g. utilizing stirred vessels. In some cases, reaction time is set much longer than kinetically needed caused by the slow mass and heat transfer in a system of low specific surface area. Replacing this equipment by a continuous flow process in a microreactor can, due to fast transport in thin fluid layers, result in notably decreased contact times. In total, the process may be carried out faster. In addition, conversion and selectivity may increase as demonstrated for metallo-organic reactions [24, 28]. Hence, space–time yields of such microreactors can exceed that of batch processes.

Intensification of Processing

Due to short diffusional distances, conversion rates can be significantly enhanced in microsystems. This was exemplarily verified for the intensification of heat transfer of thermally coupled high-temperature reactions by recent calculations [44]. For a given chemical process, using conventional technology and a microreactor, calculations predict that the amount of catalyst needed can be decreased by miniaturization by nearly a factor of 1000. This increase in performance was gained at the expense of a decrease of the ratio of reactor volume to construction material in case of the microreactor. Nevertheless, the microreactor size could be decreased by a factor of 10 compared with conventional technology, rendering its performance superior for this specific application.

Safety Issues

In the past, several examples of processing in microreactors clearly demonstrated safe operation using process parameters of otherwise explosive regimes [46–48]. This information cannot be used for classical process development, aiming at an increase of reactor size. The production inevitably has to be achieved by numbering-up of identical units, i.e. keeping the individual reaction units small. The use of operating conditions, corresponding to so far "remote" or "secret" regimes, certainly expands the operational flexibility of conventional reactors. Currently, the importance of this expansion cannot put in concrete terms, if being more restricted to model reactions, e.g. contacting hydrogen and oxygen, or being a general concept for several examples of use.

Change of Product Properties

So far, only the influence of transport intensification on conversion rate, conversion and selectivity was discussed. This holds as far as the synthesis of low-molecular weight molecules is concerned. Taking into account polymer and multiphase formation, conformational and compositional features become important as well as morphological properties, e.g. as given for the generation of supramolecular structures such as liposomes, capsules and microemulsions. These features are sensitive particularly to micromixing phenomena designating microsystems for application in these fields. Highly efficient and homogeneous mass transfer in micromixers was demonstrated to improve the uniformity of the weight distribution of polymers [41] and size distribution of droplets in semi-solid pastes [49].

Distributed Production

At present, production is carried out in large plants and it is aimed to make them larger as far as technically feasible. Concerning petrochemistry, for example, the contents of natural feedstocks are transported, sometimes over long distances, to a central plant and converted therein to more valuable products. The small size and remote location of a vast number of feedstocks render exploitation not profitable since neither plant construction nor transport in pipelines is economically attractive. Processing in microreactors may be less costly than applying conventional equipment. Installation and removal may be sufficiently fast and flexibility towards productivity high due to the numbering-up assembly.

Other examples of processes which potentially could benefit from a distributed production were given by many authors [2, 45, 50]. Most often, reactions with extremely toxic substances or otherwise hazardous potential were mentioned.

These potential features illustrate that microreactors are promising tools for on-site and on-demand production.

1.4 References

[1] Ehrfeld, W., Hessel, V., Haverkamp, V.: *"Microreactors"*, *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, (1999).

[2] Leroux, J. J., Harold, M. P., Ryley, J., Ashmead, J., O'Brien, T. C., Johnson, M., Perrotta, J., Blaisdell, C. T., Rensi, T. A., Nyquist, J.: *"Microfabricated mini-chemical systems: technical feasibility"*, in Ehrfeld, W. (Ed.) *Microsystem Technology for Chemical and Biological Microreactors*, Vol. 132, pp. 51–69, Verlag Chemie, Weinheim, (1996).

[3] Weber, L.: *"Kombinatorische Chemie – Revolution in der Pharmaforschung?"*, Nachr. Chem. Tech. Lab. **42**, pp. 698–702, 7 (1994).

[4] Balkenhohl, F. von dem Bussche-Hünnefeld, C., Lansky, A., Zechel, C.: *"Kombinatorische Synthese niedermolekularer organischer Verbindungen"*, Angew. Chem. **108**, pp. 2437–2488 (1996).

[5] Jung, G., Beck-Sickinger, A. G.: *"Methoden der multiplen Peptidsynthese und ihre Anwendungen"*, Angew. Chem. **104**, pp. 375–500, **4 (1992).**

[6] Harrison, D. J., Fluri, K., Seiler, K., Fan, Z., Effenhauser, C. S., Manz, A.; Science 261, p. 895 (1993).

[7] Widmer, H. M.: *"A survey of the trends in analytical chemistry over the last twenty years, emphasizing the development of TAS and μTAS"*, in Widmer, E., Verpoorte, E., Banard, S. (Eds.) *Proceedings of the 2nd International Symposium on Miniaturized Total Analysis Systems, μTAS'96 – Special Issue of Analytical Methods & Instrumentation AMI*, pp. 3–8, Basel, (1996).

[8] Van den Berg, A., Bergveld, P.: *"Development of μTAS concepts at the MESA Research Institute"*, in Widmer, E., Verpoorte, E., Banard, S. (Eds.) *2nd International Symposium on Miniaturized Total Analysis Systems, μTAS'96 – Special Issue of Analytical Methods & Instrumentation AMI*, pp. 9–15, Basel, (1996).

[9] Ramsey, J. M.: *"Miniature chemical measurement systems"*, in Widmer, E., Verpoorte, E., Banard, S. (Eds.) *Proceedings of the 2nd International Symposium on Miniaturized Total Analysis Systems, μTAS'96 – Special Issue of Analytical Methods & Instrumentation AMI*, pp. 24–27, Basel, (1996).

[10] Northrup, M. A., Benett, B., Hadley, D., Stratton, P., Landre, P.: *"Advantages afforded by miniaturization and integration of DNA analysis instrumentation"*, in Ehrfeld, W. (Ed.) *Microreaction Technology, Proceedings of the 1st International Conference on Microreaction Technology, IMRET 1*, pp. 278–288, Springer Verlag, Berlin, (1997).

[11] Woolley, A. T., Mathies, R. A.: *"Ultra-high-speed DNA fragment separations using microfabricated capillary array electrophoresis chips"*, Proc. Natl. Acad. Sci. USA **91**, (1994) 11348–11352.

[12] Van der Schoot, B. H., Verpoorte, E. M. J., Jeanneret, S., Manz, A., de Rooij, N. L.: *"Microsystems for analysis at flowing solutions"*, in Proceedings of the "Micro Total Analysis Systems, μTAS '94", 1994, pp. 181–196, Twente, Netherlands.

[13] Manz, A.: *"The secret behind electrophoresis microstructure design"*, in Widmer, E., Verpoorte, E., Banard, S. (Eds.) *Proceedings of the 2nd International Symposium on Miniaturized Total Analysis Systems, µTAS96 Special Issue of Analytical Methods & Instrumentation AMI*, pp. 28–30, Basel, (1996).
[14] Köhler, J. M., Dillner, U., Mokansky, A., Poser, S., Schulz, T.: *"Micro channel reactors for fast thermocycling"*, in Ehrfeld, W., Rinard, I. H., Wegeng, R. S. (Eds.) *Process Miniaturization: 2nd International Conference on Microreaction Technology, Topical Conference Preprints*, pp. 241–247, AIChE, New Orleans, USA, (1998).
[15] Lottspeich, F.: *"Proteomanalyse – ein Weg zur Funktionsanalyse von Proteinen"*, Angew. Chem. **111**, 17 (1999) 2630–2647.
[16] Manz, A., Becker, H.: *"Microsystem Technology in Chemistry and Life Science"*, *Topics in Current Chemistry*, Vol. 194, Springer-Verlag, Heidelberg, (1998).
[17] Suckling, C. J.: *"Host-guests binding by a simple detergent derivative, to mach molecules"*, J. Chem. Soc., Chem. Commun., pp. 661–662 (1982).
[18] Barrer, B.: *"Chemical nomenclature and formulation of compositions of synthetic and natural zeolites"*, Pure Appl. Chem. **51**, pp. 1091–1100 (1979).
[19] Drzaj, R.: *"Zeolites, synthesis, structure, technology and application"*, in Proceedings of the "Int. Symp. on Synthesis of Zeolites, their Structure Determination and their Technological Use", 1985, Ljubljana.
[20] Eikentscher, H., Gerrns, H., Schuller, H.: Angew. Chem. **72**, pp. 856–864 (1960).
[21] Schubert, K., Bier, W., Brandner, J., Fichtner, M., Franz, C., Linder, G.: *"Realization and testing of microstructure reactors, micro heat exchangers and micromixers for industrial applications in chemical engineering"*, in Ehrfeld, W., Rinard, I. H., Wegeng, R. S. (Eds.) *Process Miniaturization: 2nd International Conference on Microreaction Technology, IMRET 2: Topical Conference Preprints*, pp. 88–95, AIChE, New Orleans, USA, (1998).
[22] Branebjerg, J., Gravesen, P., Krog, J. P., Nielsen, C. R.: *"Fast mixing by lamination"*, in Proceedings of the "IEEE-MEMS '96", 12–15 Febr., 1996; pp. 441–446; San Diego, CA.
[23] Knight, J. B., Vishwanath, A., Brody, J. P., Austin, R. H.: *"Hydrodynamic focussing on a silicon chip: mixing nanoliters in microseconds"*, Phys. Rev. Lett. **80**, p. 3863, 17 (1998).
[24] Hessel, V., Ehrfeld, W., Golbig, K., Haverkamp, V., Löwe, H., Storz, M., Wille, C., Guber, A., Jähnisch, K., Baerns, M.: *"Gas/liquid microreactors for direct fluorination of aromatic compounds using elemental fluorine"*, in Ehrfeld, W. (Ed.) *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proceedings of IMRET 3*, pp. 526–540, Springer-Verlag, Berlin, (2000).
[25] Hessel, V., Ehrfeld, W., Herweck, T., Haverkamp, V., Löwe, H., Schiewe, J., Wille, C., Kern, T., Lutz, N.: *"Gas/liquid microreactors: hydrodynamics and mass transfer"*, in Proceedings of the "4th International Conference on Microreaction Technology, IMRET 4", pp. 174–187; 5–9 March, 2000; Atlanta, USA.
[26] Herskowits, D., Herskowits, V., Stephan, K.: *"Characterization of a two-phase impinging jet absorber II. absorption with chemical reaction of CO_2 in NaOH solutions"*, Chem. Engin. Sci. **45**, pp. 1281–1287 (1990).
[27] Chambers, R. D., Spink, R. C. H.: *"Microreactors for elemental fluorine"*, Chem. Commun., pp. 883–884 (1999).
[28] Krummradt, H., Kopp, U., Stoldt, J.: *"Experiences with the use of microreactors in organic synthesis"*, in Ehrfeld, W. (Ed.) *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proceedings of IMRET 3*, pp. 181–186, Springer-Verlag, Berlin, (2000).
[29] Cong, P., Doolen, R. D., Fan, Q., Giaquinta, D. M., Guan, S., McFarland, E. W., Poojary, D. M., Self, K., Turner, H. W., Weinberg, W. H.: *"Kombinatorische Parallelsynthese und Hochgeschwindigkeitsrasterung von Heterogenkatalysator-Bibliotheken"*, Angew. Chem. **111**, p. 508, 4 (1999).
[30] Jandeleit, B., Schaefer, D. J., Powers, T. S., Turner, H. W., Weinberg, W. H.: *"Kombinatorische Materialforschung und Katalyse"*, Angew. Chem. **111**, p. 2649, 17 (1999).
[31] Zech, T., Hönicke, D., Lohf, A., Golbig, K., Richter, T.: *"Simultaneous screening of catalysts in microchannels: methodology and experimental setup"*, in Ehrfeld, W. (Ed.) *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proceedings of IMRET 3*, pp. 260–266, Springer-Verlag, Berlin, (2000).
[32] Rodemerck, U., Ignaszewski, P., Lucas, M., Claus, P., Baerns, M.: *"Parallel synthesis and testing of heterogeneous catalysts"*, in Ehrfeld, W. (Ed.) *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proceedings of IMRET 3*, pp. 287–293, Springer-Verlag, Berlin, (2000).
[33] Danielson, E., Golden, J. H., McFarland, E. W., Reaves, C. M., Weinberg, W. H., Wu, X. D.: Nature **389**, pp. 944–948 (1997).

[34] Cong, P., Doolen, R. D., Fan, Q., Giaquinta, D. M., Guan, S., McFarland, E. W., Poojary, D. M., Self, K., Turner, H. W., Weinberg, W. H.: Angew. Chem. (Int. Ed.) **38**, pp. 484–488 (1999).

[35] Senkan, S. M., Ozturk, S.: "*Entdeckung und Optimierung von Heterogenkatalysatoren durch kombinatorische Chemie*", Angew. Chem. **111**, p. 867, 6 (1999).

[36] Results of IMM, unpublished

[37] de Bellefon, C., Tanchoux, N., Caravieilhes, S., Hessel, V.: "*New reactors for liquid-liquid catalysis*", in Proceedings of the "Entretiens Jaques Cartier", 6–8 Dec., 1999, Lyon.

[38] de Bellefon, C., Caravieilhes, S., Joly-Vuillemin, C., Schweich, D., Berthod, A.: "*A liquid-liquid plug flow continuous reactor for the investigation of catalytic reactions: the centrifugal partition chromatograph*", Chem. Eng. Sci. **53**, p. 71–74, 1 (1998).

[39] Ehrfeld, W., Golbig, K., Hessel, V., Löwe, H., Richter, T.: "*Characterization of mixing in micromixers by a test reaction: single mixing units and mixer arrays*", Ind. Eng. Chem. Res. **38**, pp. 1075–182, 3 (1999).

[40] Wörz, O., Jäckel, K. P., Richter, T., Wolf, A.: "*Microreactors, new efficient tools for optimum reactor design*", *Microtechnologies and Miniaturization, Tools, Techniques and Novel Applications for the BioPharmaceutical Industry*, IBC's 2nd Annual Conference: Microtechnologies and Miniaturization, Frankfurt, Germany, (1998).

[41] Bayer, T., Pysall, D., Wachsen, O.: "*Micro mixing effects in continuous radical polymerization*", in Ehrfeld, W. (Ed.) *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proceedings of IMRET 3*, pp. 165–170, Springer-Verlag, Berlin, (2000).

[42] Srinivasan, K., I-Ming Hsing, Berger, P., Jensen, E. K. F., Firebaugh, S. L., Schmidt, M. A., Harold, M. P., Lerou, J. J., Ryley, J. F.: "*Micromachined reactors for catalytic partial oxidation reactions*", AIChE J. **43**, pp. 3059–3069, 11 (1997).

[43] Hessel, V., Ehrfeld, W., Golbig, K., Hofmann, C., Jungwirth, S., Löwe, H., Richter, T., Storz, M., Wolf, A., Wörz, O., Breysse, J.: "*High temperature HCN generation in an integrated Microreaction system*", in Ehrfeld, W. (Ed.) *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proceedings of IMRET 3*, pp. 151–164, Springer-Verlag, Berlin, (2000).

[44] Hardt, S., Ehrfeld, W., vanden Bussche, K. M.: "*Strategies for size reduction of microreactors by heat transfer enhancement effects*", in Proceedings of the "4th International Conference on Microreaction Technology, IMRET 4", 5–9 March, 2000; Atlanta, USA.

[45] Rinard, I. H.: "*Miniplant design methodology*", in Ehrfeld, W., Rinard, I. H., Wegeng, R. S. (Eds.) *Process Miniaturization: 2nd International Conference on Microreaction Technology; Topical Conference Preprints*, pp. 299–312, AIChE, New Orleans, USA, (1998).

[46] Hagendorf, U., Janicke, M., Schüth, F., Schubert, K., Fichtner, M.: "*A Pt/Al_2O_3 coated microstructured reactor/heat exchanger for the controlled H_2/O_2-reaction in the explosion regime*", in Ehrfeld, W., Rinard, I. H., Wegeng, R. S. (Eds.) *Process Miniaturization: 2nd International Conference on Microreaction Technology; Topical Conference Preprints*, pp. 81–87, AIChE, New Orleans, USA, (1998).

[47] Veser, G., Friedrich, G., Freygang, M., Zengerle, R.: "*A modular microreactor design for high-temperature catalytic oxidation reactions*", in Ehrfeld, W. (Ed.) *Microreaction Technology: 3rd International Conference on Microreaction Technology, Proceedings of IMRET 3*, pp. 674–686, Springer-Verlag, Berlin, (2000).

[48] Ehrfeld, W., Hessel, V., Löwe, H.: "*Extending the knowledge base in microfabrication towards chemical engineering and fluid dynamic simulation*", in Proceedings of the "4th International Conference on Microreaction Technology, IMRET 4", 5–9 March, 2000; Atlanta, USA.

[49] Hessel, V., Ehrfeld, W., Haverkamp, V., Löwe, H., Schiewe, H.: "*Dispersion Techniques for Laboratory and Industrial Production*", in Müller, R. H. (Ed.) Apothekerverlag, Stuttgart, (1999); in press

[50] Ponton, J. W.: "*Observations on hypothetical miniaturised disposable chemical plant*", in Ehrfeld, W. (Ed.) *Microreaction Technology, Proceedings of the 1st International Conference on Microreaction Technology, IMRET 1*, pp. 10–19, Springer-Verlag, Berlin, (1997).